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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,964	11/21/2000	Michael E. O'Donnell	22221/1030 (RU-339 CIP)	2211

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Michael L. Goldman
NIXON PEABODY LLP
Clinton Square
P.O. Box 31051
Rochester, NY 14603

EXAMINER
HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/716,964	O'DONNELL ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-70* is/are pending in the application.

4a) Of the above claim(s) *4-6 and 10-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3,7 and 9* is/are rejected.

7)☐ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 November 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-70 are still at issue and are present for examination.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1-15 and 49-56, B (encoding delta subunit of *Thermus thermophilus*) in Paper No. 9, 9/9/2002, is acknowledged. The traversal is on a number of ground(s). Firstly applicants submit that the inventions of Groups I and II are related inventions, i.e., both relate to polymerase subunits that are capable of use together to form a clamp loader of a polymerase III enzyme. Applicants characterization of the relationship between the inventions of Groups I and II is found persuasive, and as applicants assert the inventions of Groups I and II are related.

Inventions I, II, III and IV are related as subcombinations disclosed as usable together in a single combination. The subcombinations are distinct from each other if they are shown to be separately usable. In the instant case, inventions I and II each have a separate utility such as their use as hybridization probes for the detection of different nucleic acid molecules and, inventions III and IV each have a separate utility such as their use in the synthesis of antibodies to be used for the detection of different polypeptide molecules.See MPEP § 806.05(d).

Applicants submit that to support restriction between related inventions, "the examiner... must show by appropriate explanation one the following: (A) Separate classification thereof...; (B) A separate status in the art when they are classifiable together...; or (C) A different field of search... " and that the examiner has failed to fulfill

his obligation in demonstrating that these inventions must be restricted. Applicants specifically support this position on the basis that each of the two inventions (Groups I and II) for which applicants traverse their separation, are each classified in the same class 435, subclass 194, which only contains approximately 84 patents to polymerases or polymerase subunits. Therefore, groups I and II should remain together, based on applicants assertion that the search for the invention of Group I and Group II would be nearly, if not completely co-extensive. This argument is not found persuasive, because as was stated previously each of restricted Groups I- IV are drawn to molecules which are structurally and chemically independent and different. Thus while the searches of each of the molecules do overlap, they are not co-extensive and applicants are reminded that the complete search of the each of the above groups is based on much more then the mere searching of those issued patents in class 435, subclass 194. A complete search involves searching many additional nucleic acid databases, polypeptide databases and text databases, such that the independent and different structures of each of the different Groups does make their search together burdensome.

Applicants correctly point out that claims 1 and 2 are generic linking claims that are each listed with the subject matter of Groups I and II.

Claims 1-3 and 49-56 link(s) inventions I and II. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claims 1 and 2. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to

examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Applicants further submit that restriction between A-D (and E-H) is improper on the basis that the various claimed species are functionally related and thus applicants should be entitled to examination of the claimed genus of delta or delta subunits. As discussed above, with respect to Groups I-IV, the species A-D (as well as E-H) are related as subcombinations capable of use together.

Inventions A-H are related as subcombinations disclosed as usable together in a single combination. The subcombinations are distinct from each other if they are shown to be separately usable. In the instant case, inventions A-H each have a separate utility such as their use as hybridization probes for the detection of different nucleic acid molecules.See MPEP § 806.05(d). Therefore, as discussed above (for Groups I-IV) inventions A-H are also restrictable.

Claims 4-6, 10-48 and 57-70 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 9.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Applicants filing of information disclosures, paper no. 10, filed 10/1/2002, is acknowledged. Those references considered have been initialed.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

The declaration identifies the provisional application to which priority is claimed as **60/143,202**, not **60/043,202.**

Drawings

The drawings are objected to for the reasons stated on the enclosed form PTO-948.

Specification

The disclosure is objected to because of the following informalities:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth: Applicants attention is drawn to the figures which contain nucleotide and/or amino acid sequences and MPEP **2422.02** - The Requirement for Exclusive Conformance; Sequences Presented in Drawing Figures

> ...It should be noted, though, that when a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequen identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings.

Specifically figures 15A and 15B contain amino acid sequences which should be describ SEQ ID NO. as discussed above.

Appropriate correction is required.

Claim Objections

Claims 8 is objected to because of the following informalities:

Claims 8 is dependent on rejected claim 7.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is indefinite in the recitation of "stringent conditions" as the specification does not define what conditions constitute "stringent". It is unclear as to the metes and bounds of what is to be included within the scope of this term and in the art what is considered stringent varies widely depending on the individual situation as well as the person making the determination. As such it is unclear how homologous to the sequence of a nucleotide sequence of SEQ ID NO. 157, a sequence must be to be included within the scope of these claims.

Claim 9 is further indefinite in that the recitation "...hybridizes to a DNA molecule comprising the nucleotide sequence of SEQ. ID. No. 157..." is unclear. Specifically it is unclear to what applicants are defining that the claimed DNA molecule must hybridize. Is it applicants intent that the claimed DNA molecule hybridize under stringent conditions to "the nucleotide sequence of SEQ. ID. No. 157" or "a DNA molecule comprising the nucleotide sequence of SEQ. ID. No. 157". It is suggested that

applicants amend the claim to "...hybridizes to the nucleotide sequence of SEQ. ID. No. 157..." in order to overcome this aspect of this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 7, 9 and 49-56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 7 and 9 are directed to all possible isolated DNA molecules from a thermophilic bacterium, wherein said DNA molecule encodes a DNA polymerase III-type enzyme subunit (claim 1), wherein the enzyme subunit is selected from the group consisting of alpha, tau, gamma, epsilon, delta, delta prime, and SSB subunits (claim 2), wherein the enzyme subunit is a delta subunit (claim 3), wherein the thermophilic bacterium is *Thermus thermophilus* (claim 7), wherein said DNA molecule hybridizes under stringent conditions to SEQ ID NO. 157 (claim 9). Claims 49-56 are directed to all possible expression systems, host cells and methods of expression of the DNA molecule according to claim 1.

The claims rejected under this statute have absolutely no structural limitations.

There is no disclosure of any particular structure to function/activity relationship in the disclosed species. The specification also fails to describe additional

representative species of these polypeptides by any identifying structural characteristics or properties other than the activities recited in the claims, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-3, 7 and 49-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DNA molecule from a thermophilic bacterium encoding a DNA polymerase III-type enzyme delta subunit, wherein said DNA molecule comprises a nucleotide sequence of SEQ ID NO. 157, does not reasonably provide enablement for any DNA molecule from a thermophilic bacterium encoding a DNA polymerase III-type enzyme delta subunit. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4)

the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-3 and 7 are so broad as to encompass any isolated DNA molecule from a thermophilic bacterium, wherein said DNA molecule encodes a DNA polymerase III-type enzyme subunit (claim 1), wherein the enzyme subunit is selected from the group consisting of alpha, tau, gamma, epsilon, delta, delta prime, and SSB subunits (claim 2), wherein the enzyme subunit is a delta subunit (claim 3) and wherein the thermophilic bacterium is *Thermus thermophilus* (claim 7). Claims 49-56 are so broad as to encompass any expression system, host cell and method of expression of the DNA molecule according to claim 1.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of DNA molecules broadly encompassed by the claims, including those yet to be discovered or identified. The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the claimed DNA molecules Since the amino acid sequence of a protein (and hence its encoding DNA) determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function.

However, in this case the disclosure is limited to that DNA molecule which comprises the amino acid sequence of SEQ ID NO: 157.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Further applicants have given no guidance where one could obtain other species encompassed by the claimed genus.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any DNA molecule from *Thermus thermophilus* which encodes a delta subunit because the specification does not establish: (A) regions of the protein structure which may be modified without effecting delta subunit activity; (B) the general tolerance of delta subunits to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a delta subunit with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the delta subunit activity and the fact that the

relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those DNA molecules of the claimed genus which encode a polypeptide with delta subunit activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any DNA molecule from a thermophilic bacterium, encoding a DNA polymerase III-type enzyme delta subunit. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned

are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
November 15, 2002